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WASHINGTON, D. C.

November 1953

VOLUME IX NUMBER 11

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CLINICAL PROCEEDINGS

OF THE CHILDREN'S HOSPITAL

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RECENT ADVANCES IN THE CHEMOTHERAPY OF LEUKEMIA AND MALIGNANT TUMORS OF CHILDREN*

E. Clarence Rice, M.D.
Jerome Bernstein, M.D.

If one includes leukemia among the malignant neoplasms affecting children and listed under the general designation of cancer, we find that such malignant disease is not rare among children.

During the years 1950–1952 there were 427 deaths at the Children's Hospital, and of these 35 were due to malignant tumors and leukemia.

Anderson and Martin (1) found that in 71,273 admissions to the Children's Hospital, Washington, D. C., that 558 or 0.78 per cent had tumors, and of these 144 or 0.2 per cent were malignant. These statistics are for children of 12 years of age or younger.

Coincident with the availability of antibiotics, intravenous fluids and blood and improved surgical technic, the problem of cancer in children has been brought into true perspective.

Fifteen years ago the number of deaths from infection were so numerous as to obscure the problems of children with malignant tumors. Because of their relative infrequency at that time, little attention was given to their treatment except on an individual basis and many physicians and surgeons worked with no very definite plan in mind. The various factors mentioned served to change our present day concepts of this problem of childhood.

The establishment of a Tumor Clinic and Tumor Board at the Children's Hospital has served to bring the problem in children into proper focus.

Leukemia stands first among the malignant neoplasms in this age group. Next come the embryonic tumors of the kidney, Wilms' tumor; followed by tumors of the sympathetic nervous system, neuroblastomas; and after this, tumors of the lymphatic system, lymphosarcoma and Hodgkin's disease. Bone tumors are not frequently seen. Brain tumors will not be discussed in this paper. The tumors of muscles, sex organs and breasts are not seen with sufficient frequency to constitute the problem that they do in adults, nor do the skin and mucous membranes give rise with any frequency to malignant tumors in children. The lack of influence of the sex glands and the fact that many of the tumors seen in children are of embryonic origin are largely responsible for the differences between the organs or tissues involved, their incidence and course in adults, children and infants.

* From the Department of Laboratories and the Tumor Clinic of the Children's Hospital, Washington, D. C. Read at the meeting of Region II, American Cancer Society, Inc., Washington, D. C., September 26, 1953.

We wish to thank the Lederle Laboratories Division of the American Cyanamid Company for their generosity in supplying the folic acid antagonists and T E M; and the Wellcome Research Laboratory for the 6-mercaptopurine.

Through the establishment of a Tumor Clinic and the Tumor Board at Children's Hospital with funds provided by the American Cancer Society, the thinking of most physicians and the planning for the treatment of cancer in infants and children has proceeded in a systematic manner, so that surgery has been able to increase its effectiveness. At the time of the organization of the Tumor Clinic and Tumor Board, there was but one patient who had been operated on for Wilms' tumor of the kidney, who had survived for any long period of time. At this time 12 out of 18 patients operated on since the formation of the Tumor Clinic and Tumor Board are alive. Ten of those living were operated on over one year ago.

While no cure has been achieved in any of our patients with cancer affecting the blood forming organs and the lymphatic system, much has been accomplished in the treatment and relief of these conditions, due to the increasing benefits which have been obtained from chemotherapy.

Nitrogen mustard (methyl bis(2-chloroethyl)amine), and tri-ethylene malamine, TEM, have been used with some benefit in the treatment of the lymphomas. TEM lends itself well to the treatment of children with Hodgkin's disease and they tolerate the drug over long periods of time. One patient with rhabdomyosarcoma responded particularly well for nearly a year when treated with nitrogen mustard. No attempt has been made to use nitrogen mustard intra-arterially. Several children with various forms of cancer have received tri-ethylenephosphoramide, TEPA, without demonstrable benefit. Radioactive gold-198 was used in treating the metastatic abdominal lesions of a boy with Wilms' tumor without benefit.

Acute leukemia is seen in both adults and children and is a fatal disease. Prior to the use of the anti-folic acid drugs the physician had little to offer these patients. The observation that folic acid and pteroylglutamic acid, caused an "acceleration phenomenon" in the viscera and bone marrow led Farber[2] to treat children with acute leukemia with folic acid antagonists. The success of the chemotherapy of acute leukemia has been greatest in the treatment of children, and, with the evolution of the various biological antagonists of folic acid, preparations of lower toxicity than the initial ones have been used. These compounds act by interfering with the action of the enzymes concerned with the conversion of folic acid to the citrovorum factor and its utilization by the cell, particularly those of the lymphocytic series. The effects in anemias are similar to those seen when folic acid is not included in the diet. The similarity of the effects of these compounds and those obtained from the use of the steroids suggests that they may act in part through such a metabolic effect. Amethopterin has proven to be relatively non-toxic, and with it complete and partial remissions in leukemia have been effected. Many other compounds have been studied by various investigators.

In addition to the use of the antifols, the recognition of the value of ACTH and cortisone has greatly aided us in the treatment of leukemia in children. These drugs will usually induce a remission in children with acute lymphocytic leukemia, although their durational effect is not as prolonged as that attained with folic acid antagonists. One of the most valuable benefits noted in the treatment of leukemia and diseases associated with thrombocytopenia and increased capillary fragility has been their effectiveness in stopping hemorrhage by rendering the capillaries less permeable to the passage of red blood cells.

The increased susceptibility to infection of patients with leukemia and the lowering of resistance while receiving the steroids, ACTH and cortisone, has made it necessary to use the antibiotics with great frequency. Those which can be given orally, aureomycin, terramycin and erythromycin, have proven to be as valuable as the antimetabolites in the treatment of leukemia; thus the present-day treatment combines the use of the antimetabolites, the steroids, ACTH and cortisone, and the antibiotics.

We have used radioactive phosphorous-32 with benefit in the treatment of one child with chronic myelocytic leukemia.

In England, Galton[3] has obtained rather promising results from myleran, 1:4 dimethanesulphomyloxybutane, in the treatment of chronic leukemia. We have had no experience with this drug.

The search for antimetabolites which might interfere with the growth of malignant cells has been wide. The importance of the purines to cell metabolism has been known for some time. Hitchings and his associates[4] have presented data indicating that the interference with nucleic acid metabolism of parasitic cells may be related closely to the effects noted when these cells are exposed to the metabolic effects of the antifols. In 1951 Burchenal and his co-workers[5] reported on the treatment of five patients with acute leukemia with 2,6-diaminopurine, an antagonist of adenine. The benefits noted from the use of this drug and the experience obtained from the use of other antimetabolites has prompted the study of other compounds in the treatment of leukemia and other forms of cancer. The experience of investigators[6] at the Memorial Center for Cancer and Allied Diseases, New York, based on the treatment of over 100 patients with a nucleic acid antagonist, 6-mercaptopurine, has been reported. They obtained good clinical and hemotological remissions in 15 out of 45 children and in another 10, partial remissions and clinical improvement were observed. This drug has proved to be a valuable adjunct to the previously established treatment of acute leukemia with antifols and steroid therapy. Some children who had become resistant to the usual drugs were benefitted by 6-mercaptopurine. It is without apparent benefit in the treatment of lymphomas and carcinomas.

We have used 6-mercaptopurine in the treatment of 12 children who have acute leukemia. While all patients have not responded favorably, some beneficial effect from the use of this drug was obtained in most of them. Like the other antimetabolites it must be administered with considerable care, as it may cause marked depression in the leukocytes and platelets through its action on the bone marrow and lymphatic system.

In view of the rarity of acute myelocytic leukemia in the newborn, and the previous hopelessness of the situation from the standpoint of treatment, the report of a patient with acute myelocytic leukemia is given:

CASE PRESENTATION

The patient, a white female, aged 11 months, was hospitalized because of enlargement of the occipital lymph nodes, splenomegaly, generalized bruising and apparent anemia. The hemoglobin was 6.4 gm. per 100 ml., with 150,000 leukocytes 99 per cent being granulocytes with 35 per cent myeloblasts. Platelets were markedly reduced. Transfusions were given, and seven days after admission, treatment with 6-mercaptopurine was begun. The initial dose was 25 mg. for four days, increasing to 50 mg. for five days, then continuing in amounts of between 25 and 37.5 mg. daily. Twenty-three days elapsed before a definite fall in the leukocyte count was apparent. At this time it dropped to 40,000 and four days later it was 9,300, myelocytes and other immature cells having been reduced to 4 per cent. Platelets were 20,000 and reticulocytes were absent. On the 27th day 6-mercaptopurine was discontinued, but cortisone, which had been given because of the bruising and hemorrhagic tendency, was continued. The bone marrow at this time contained few immature granulocytes but a marked increase in lymphocytes was noted. The leukoid-erythroid ratio was now 5:1 as compared with one of 60:1 at the time of admission to the hospital. Erythromycin was given for a carbuncle in the occipital region. Improvement followed. Cortisone was discontinued after three weeks of administration. Fifty-eight days after 6-mercaptopurine had been started, and 21 days following its discontinuance, the leukocyte count was 9,500 with 28 per cent granulocytes. Platelets at this time averaged 100,000. The bone marrow now showed a marked depression of the granulocytic cells; however many megakarocytes were now present. Up to this time transfusions of freshly drawn blood from plastic containers had been given at frequent intervals because of the anemia, thrombocytopenia and infection. Seventy-one days after 6-mercaptopurine therapy had been instituted the leukocyte count was 8,700, with 8 per cent granulocytes, 85 per cent lymphocytes and 7 per cent monocytes; bone marrow activity was marked with 32 per cent granulocytes, 13 per cent being myelocytes or more immature cells. The leukoid-erythroid ratio was 0.8:1, erythroblasts were numerous and many megakarocytes were present. The cervical lymph nodes were moderately enlarged, and the spleen could be felt 5 cm. below the rib margin. The patient's general condition could be described as fair.

This case is reported not as a cure, but because the results obtained in the treatment of a young child with acute myelocytic leukemia with 6-mercaptopurine have exceeded our expectations and may point the way to better therapeutic benefits in the future.

More recently two of our patients with acute lymphocytic leukemia, who have ceased to be benefitted by treatment with amethopterin, 6-mer-

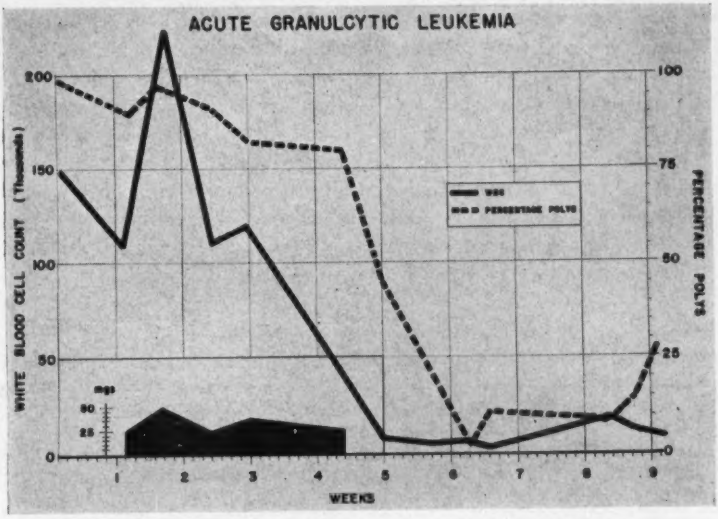
ACUTE GRANULCYTIC LEUKEMIA
WHITE BLOOD CELL COUNT (Thousands)
PERCENTAGE POLYS
WEEKS
200
150
100
50
0
100
75
50
25
0
1
2
3
4
5
6
7
8
9

FIG. 1

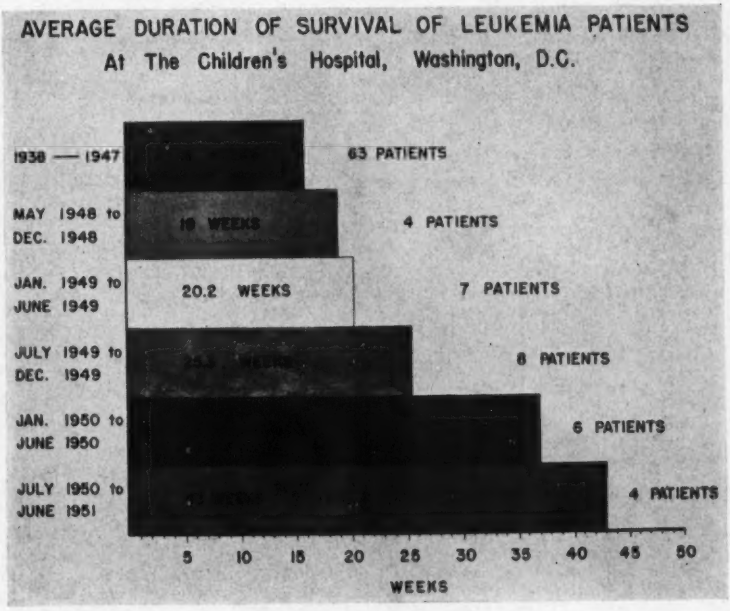
AVERAGE DURATION OF SURVIVAL OF LEUKEMIA PATIENTS
At The Children's Hospital, Washington, D.C.
1938 — 1947
63 PATIENTS
MAY 1948 to DEC. 1948
19 WEEKS
4 PATIENTS
JAN. 1949 to JUNE 1949
20.2 WEEKS
7 PATIENTS
JULY 1949 to DEC. 1949
8 PATIENTS
JAN. 1950 to JUNE 1950
6 PATIENTS
JULY 1950 to JUNE 1951
4 PATIENTS
5
10
15
20
25
30
35
40
45
50
WEEKS

FIG. 2

captopurine and cortisone have achieved remissions by the combined use of 6-mercaptopurine and a new preparation known as P-165. Inasmuch as this therapy is being given elsewhere, we are not at liberty to make any further report on this combined treatment, except to state that it has changed a hopeless situation to one of renewed hope for these two patients.

Examination of Figure 2 will show an increasing survival time for our patients during a 22-year period. Initially the use of antifols increased the duration of life a little, but with the use of less toxic compounds, the steroids, the oral use of antibiotics and now various purine derivatives, the average span has been prolonged from 16 weeks to 43 weeks.

TABLE I

Leukemia Patients Living—Children's Hospital, Washington, D. C., September 26, 1953

NO. OF PATIENTS	DURATION (weeks)	CONDITION
1	13	Good
2	22	Good
1	25	Good
2	41	Good
1	54	Fair
1	61	Good
8		

Thus, it is evident that those who treat malignant tumors in children have not achieved any successes beyond those obtained in adults with chemotherapy. However, the benefits in the treatment of acute leukemia in children show a gradual improvement which is encouraging, and brings renewed hope to both physician and parent.

REFERENCES

1. Anderson, R. H. and Martin, M. B.: Analysis of All Tumors at Children's Hospital Over a Ten-Year Period. *Clin. Proc., Children's Hosp.* **7**: 64 (February) 1951.
2. Farber, S.: Some Observations on the Effect of Folic Acid Antagonists on Acute Leukemia and Other Forms of Incurable Cancer. *Blood* **4**: 160 (February) 1949.
3. Galton, D. A. G.: Myleran in Chronic Myeloid Leukemia. *Lancet* i, 208 (Jan. 31) 1953.
4. Hitchings, G. H., Elion, G. B., Falco, E. A., Russell, P. B. and Vanderwerff, H.: Studies on Analogs of Purines and Pyrimidines. *Ann. New York Acad. Sc.* **52**: 1318 (July) 1950.
5. Burchenal, J. H., Karnofsky, D. A., Kingsley-Pillers, E. M., Southam, C. M., Myers, W. P. L., Escher, G. C., Craver, L. F., Dargeon, H. W. and Rhodes, C. P.: *Cancer* **4**: 549 (May) 1951.
6. Burchenal, J. H. Murphy, M. L., Ellison, R. R., Sykes, M. P., Tan, T. C., Leon, L. A., Karnofsky, D. A., Craver, L. F., Dargeon, H. W. and Rhodes, C. P.: *Blood* (To be published)

LEAD ENCEPHALOPATHY COMPLICATED BY RESPIRATORY CENTER DEPRESSION

Special Report No. 275

Roger Bergstrom, M.D.
Stanley I. Wolf, M.D.
Samuel Bessman, M.D.

D. H., a two year old colored female, was admitted to the Children's Hospital two hours after a convulsion which occurred at home. The patient had apparently been well until the day of admission when she developed anorexia and vomited one time. Prior to the convulsion the child had been completely afebrile. There was no history of head injury, exposure to contagious disease or drug ingestion.

Past history revealed that the patient frequently put objects into her mouth.

Physical examination on admission revealed a well-developed, well-nourished, colored female lying in bed in no distress. Temperature was 99.6 degrees; pulse, 80; respiration, 21; and blood pressure, 98/60. Ears, eyes, nose, and throat were normal except for minimal pharyngeal injection. Examination of chest and abdomen disclosed no abnormalities. The skin was dry, and there were no abnormalities present.

Neurological examination revealed slight, but definite nuchal rigidity. Deep tendon reflexes were hyperactive and equal bilaterally. No abnormal reflexes were present.

Laboratory studies on admission revealed a hemoglobin 2 grams, red blood cells 2,700,000, white blood cells 10,200 with segmented forms 57, band forms 3, lymphocytes 38, monocytes 1, and basophils 1.

Urinalysis, sickling test, and serology were negative.

Examination of spinal fluid: Lumbar puncture showed white blood cells 4, protein 60 milligrams, sugar 50 milligrams, chlorides 695 milligrams. Fasting blood sugar was 75 milligrams per 100 milliliters, phosphorus 3.9 milligrams per 100 milliliters, and calcium 9.5 milligrams. PPD #1 was negative.

HOSPITAL COURSE

During the first four days in the hospital the patient had no convulsive seizures. It was not until the third hospital day that a history was elicited that the child had eaten chips of paint from a screen door and porch railing. Roentgenograms of the lower extremities revealed increased densities at the metaphyses of the distal ends of both femora and of the metaphyses of the distal and proximal ends of both tibiae and fibulae which suggested heavy metal poisoning. This evidence, plus the finding of basophilic stippling of red blood cells, and the history of paint ingestion confirmed the impression of lead poisoning. She ate well and appeared normal except for occasional episodes of vomiting. A catheterized 12 hour urine showed lead excretion consistent with a diagnosis of plumbism.

The morning of the fifth hospital day she was noted to be restless. She refused her breakfast and seemed very apathetic. Because the patient's condition appeared to be worsening, calcium disodium ethylenediamine tetraacetate, 1 gram in 50 milliliters 5 per cent glucose in distilled water, was given intravenously, after the 12 hour urine, rather than after a full 24 hours. Approximately 90 minutes later a severe generalized convulsion, more marked on right side, occurred. This was controlled by giving 2 grains (0.130 grams) of sodium luminal and oxygen by inhalation. Respirations became shallow soon after this, and the patient's respirations were stimulated for 15 minutes with the electrophrenic respirator via the finger electrode. One hour later,

when convulsive twitchings again were noted, sodium luminal, grains 1 (0.060 grams) was given intravenously, and again respiration ceased. Artificial respiration followed by electrophrenic respirator stimulation was necessary. Within the next six hours this pattern was repeated three times, and it was decided that continuous phrenic stimulation was indicated. Accordingly, the patient was sent to the operating room and an electrophrenic electrode was inserted around the right phrenic nerve. Continuous stimulation was then used for approximately four 2–15 minute intervals throughout the day and night until the seventh hospital day (approximately 36 hours). During the non-stimulated periods breathing was very slow and irregular, and on one occasion it ceased completely. Calcium disodium ethylenediamine tetraacetate, 0.250 gram in 50 milliliters 5 per cent dextrose in water, was administered intravenously six hours after the first dose and was continued in this dosage every six hours for the next four days for a total of 4.50 grams.

After insertion of the electrode the patient continued to have mild intermittent convulsive movements of the right arm and both legs despite the administration of ½ grain (.030 gram) sodium luminal intravenously every four hours. On the sixth hospital day the patient developed a pulse rate of 104 and an arrhythmia. Electrocardiogram and cardiac consultation revealed no evidence of cardiac abnormality or heart failure. Carbon dioxide combining power at this time was 58 volumes per cent. The patient was comatose and did not respond to stimulation. Clear spinal fluid was obtained under 580 milliliters of water pressure and the excess fluid was slowly drained off. The protein content was 31 milligrams per cent, sugar 82 milligrams per cent, white blood cells 1 per cubic millimeter. The patient's condition remained poor throughout that night but on the morning of the seventh hospital day she opened her eyes and spoke a few one syllable words. Spinal puncture revealed a pressure of 600 milliliters and the excess fluid was again slowly drained off. The patient now received sodium luminal grain ½ (0.030 gram) every six hours intravenously and no further convulsive seizures were noted. The electrophrenic respirator was in use up to noon of the seventh day. At this time the deep tendon reflexes were normal bilaterally. By the evening of the seventh day the patient was taking food from a cup and eating soft baby food. Spinal fluid obtained on the eighth and ninth days was under a pressure of 240 milliliters, and again the excess fluid was drained off slowly. The patient continued to make steady improvement. The electrode was removed from the neck on the tenth hospital day. Two weeks later she was discharged from the hospital showing no evidence of residual brain damage.

DISCUSSION

Dr. Samuel Bessman:

This case represents a fairly complicated picture of lead encephalopathy. The initial convulsive episodes, followed by almost complete spontaneous disappearance of symptoms and a further recrudescence of encephalopathic symptoms, is not uncommon. A similar case was reported from this hospital[1]. Since the diagnosis of lead poisoning was tentatively confirmed by x-ray findings on the fourth hospital day, a plan of experimental therapy was instituted to test the effect of calcium disodium ethylenediamine tetraacetate in what was then considered a mild case of this disease. A twelve-hour urine was collected initially and the medication was started as per

schedule. During the first twenty-four hour period, through the fourth and fifth hospital days, the patient's condition gradually worsened and culminated in the convulsive episode shortly after the initiation of therapy. In view of our experience with the first case treated with this medication, we were convinced that the convulsions were not due to the therapy, and continued the administration of the chelating agent. The course of the patient subsequently justified this decision, and it can now be seen that severe cerebral edema was probably the cause of the cerebral symptoms. The data on the lead content of blood and urine and the enhancement of excretion by therapy will be reported elsewhere.

An important feature of this case is the use of the electrophrenic respirator to tide the patient over the periods of respiratory failure which apparently resulted from the cerebral edema. The use of repeated spinal taps to diminish the intracranial pressure has been recommended as a therapeutic procedure in acute lead encephalopathy, and appeared to be beneficial in this patient, as well as in the one referred to above. The possibility that the 2 grains of sodium amytal administered to this child on the fifth hospital day might have been the cause of the respiratory depression was considered unlikely, particularly in view of the fact that additional sodium luminal was given to control subsequent cortical hyperactivity. It is our impression in retrospect that this was not the etiological factor in the respiratory abnormality, but that it could be satisfactorily explained on the basis of the marked cerebral edema as evidenced by the greatly increased spinal fluid pressure.

SUMMARY

1. A case of lead encephalopathy is reported which began with mild convulsive seizure and became relatively asymptomatic, followed by a severe recrudescence of symptoms during observation.

2. Respiratory failure was treated with the electrophrenic respirator with satisfactory results.

3. The patient was deleaded with calcium disodium ethylenediamine tetraacetate.

REFERENCES

1. Bessman, S. P., Ried, H. and Rubin, M.: Treatment of Lead Encephalopathy with Calcium Disodium Versenate, *Med. Annals of D. C.* Vol. XXI, No. 6, June, 1952.

2. Rubin, M., Solange, G., Bessman, S. P. and Belknap, E. L.: Enhancement of Lead Excretion in Humans by Disodium Calcium Ethylenediamine Tetraacetate, *Science*, Vol. 117, No. 3050, 659-660, June 12, 1953.

CAT SCRATCH DISEASE IN CHILDREN

(A Report of Five Cases)

Theodore Winship, M.D.*

Since attention was first called to cat scratch disease[1] in 1950, more than 200 cases have been reported from all over the world. It is probably not a new disease entity for clinically similar cases have been seen for many years but they have been referred to by various terms. In the past, cat scratch disease has been mistaken clinically for tuberculosis, lymphopathia venereum, tularemia and infectious mononucleosis. It has also been confused with lymphosarcoma, Hodgkin's disease and other malignant tumors[2–5].

Many of the patients with cat scratch disease are children because of their frequent contact with cats. Five cases which have been treated at Children's Hospital during the past two years illustrate the clinical aspects of cat scratch disease.

CASE REPORTS

Case 1: W. T., a six year old white girl was admitted to Children's Hospital on December 28, 1952 for the removal of a tumor on her arm. A tender nodule had been present on the medial aspect of the left elbow for one month. It was a firm 3 cm. rounded mass which appeared to be attached to the median nerve. Her white blood count was 14,400 with 55 per cent polymorphonuclear leucocytes and 43 per cent lymphocytes. Her temperature was 99.5. The nodule was removed on December 29, 1952 and the following day a histologic diagnosis of cat scratch disease was established. On January 5, 1953 she was tested with cat scratch antigen and within 48 hours she developed an area of erythema measuring 3 x 2.5 cm. Following this she was treated with aureomycin for 10 days. The patient made an uneventful recovery.

Case 2: L. L., a two year old white girl was admitted to Children's Hospital on December 27, 1952 for the treatment of fever and a gradually enlarging tender nodule in the left submaxillary triangle. The child had received courses of both streptomycin and penicillin without beneficial effects. On admission the temperature was 102 and the white blood count was 13,000 with 62 per cent polymorphonuclear leucocytes and 34 per cent lymphocytes. On January 2, 1953 the nodule was incised and a large amount of pus was obtained. Fragments of tissue removed at this time were found to be consistent histologically with cat scratch disease. On January 6, 1953, the child was tested with cat scratch antigen and the test was read as positive two days later. The site of inoculation was not discovered. Three months later she had fully recovered.

Case 3: O. R., a seven year old white boy was admitted to Children's Hospital on December 20, 1952 for the excision of a non-tender axillary lymph-node which had been present for 10 days. The white blood count was 9,400 with 40 per cent polymorphonuclear leucocytes and 44 per cent lymphocytes. His temperature was 99.4. He had received penicillin for four days prior to admission without benefit. The

* Department of Laboratories, Children's Hospital, Washington, D. C.

histologic diagnosis on the excised node was cat scratch disease. A history of contact with a cat was subsequently elicited and the skin test was positive. The child had fully recovered without further therapy three weeks after the diagnosis was established.

Case 4:* P. W., a four year old white girl was admitted to Children's Hospital on December 13, 1950. Her mother had noticed a firm non-tender mass in the region of the right sternoclavicular joint ten days before admission. The child was afebrile and her white blood count was 6,400 with 37 per cent polymorphonuclear leucocytes and 61 per cent lymphocytes. A diagnosis of chondrosarcoma was suggested. At

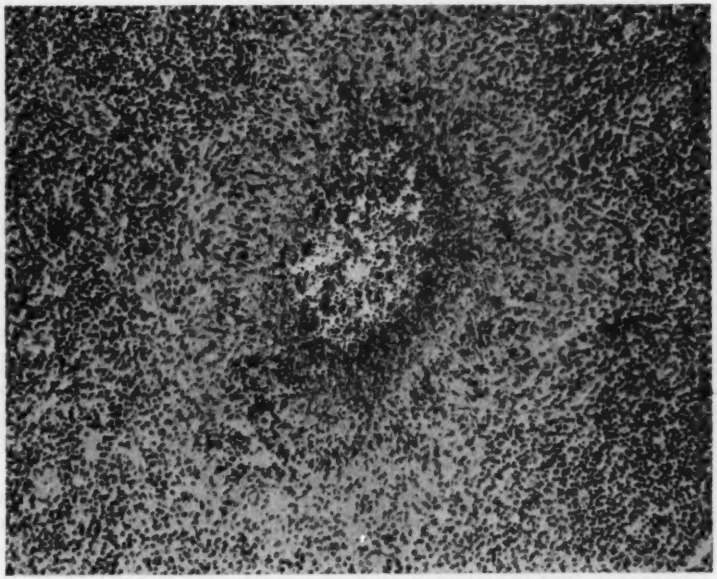

FIG. 1. A well-developed abscess in a lymph node from Case No. 3. Note the central area of necrosis and the palisading zone of epithelioid cells. Hematoxylin and eosin; enlarged 100 times.

operation a portion of the lower end of the sternocleidomastoid muscle was removed with an adjacent lymph node. A frozen section report was "malignant tumor". The following day a diagnosis of cat scratch disease was established on paraffin sections. An intradermal test with cat scratch antigen was subsequently positive. A confirmatory history of association with cats was established, but no skin lesion was observed while the patient was in the hospital.

Case 5: J. S., a thirteen year old white boy was admitted to Children's Hospital on October 24, 1953 for the excision of left epitrochlear lymph nodes for diagnosis. These nodes were tender and measured 6 cm. in diameter. The axillary nodes were

* This case was previously reported. (8)

palpable bilaterally but were moderately enlarged and tender on the left. The spleen was palpable 3 cm. below the costal margin. The temperature was 98.8. The white blood count was 8,800 with 44 per cent polymorphonuclear leucocytes and 40 per cent lymphocytes. The patient had suffered from a "cold" four weeks before admission. This lasted for several days and was accompanied by a temperature of 100 and general malaise. The enlarged lymph nodes became apparent two weeks later. A diagnosis of lymphoma was considered because of the splenomegaly but a history of close association with numerous cats was elicited. No primary site of inoculation was observed. The histologic diagnosis on the excised lymph nodes was cat scratch disease. The skin test was strongly positive. One week later the spleen had decreased in size and the child was apparently well. Splenomegaly has not been reported as a physical finding associated with cat scratch disease.

CLINICAL AND PATHOLOGIC ASPECTS

Sometimes there are no systemic manifestations of cat scratch disease but in most instances it is characterized by fever and malaise. Localized manifestations of the disease may occur as Parinaud's oculoglandular syndrome[6] or encephalitis[7]. Occasionally a macular or papular rash develop early in the course of the disease, but it lasts briefly. In approximately half the cases there is a cutaneous lesion at the site of the scratch which develops a crust and heals. This is followed in one to three weeks by regional lymphadenopathy without lymphangitis. The most common sites of lymphadenopathy are the axillary, epitrochlear, femoral, inguinal and the cervical regions. The nodes may be mobile and nontender or they may become fixed and painful. Suppuration sometimes ensues and the disease may last several weeks to several months. The lymph nodes removed from patients with cat scratch disease are frequently dissected out with difficulty because of the involvement of the pericapsular tissue.

A detailed study of lymph nodes from a large series of cases[9–10] has shown a progression of the destructive process beginning with minute microabscesses which develop into large confluent abscesses. The abscesses contain chiefly polymorphonuclear leucocytes and debris, but no caseous material. About the necrotic areas are thick collars of epithelioid cells usually arranged in a palisade fashion. Langhan or Sternberg type giant cells are sometimes present in or near the collar of epithelioid cells but they are not invariably present. Small purple inclusion bodies are found within the numerous enlarged macrophages by the use of Giemsa stains, but these have also been found in Giemsa stained sections of many granulomatous diseases, so they cannot be considered specific for cat scratch disease [10]. The histologic appearance of the lymph nodes, while not pathognomatic, is suggestive of cat scratch disease but may be mistaken for tularemia, lymphopathia venereum or tuberculosis.

Antigen for the skin test may be prepared, according to the method devised by Hanger and Rose[2], using pus aspirated from a suppurating

lymph node in a patient with known cat scratch disease. The material is diluted one part to five parts with isotonic sodium chloride solution and heated at 56 degrees C. for one hour on two successive days. The intradermal test is performed by injecting 0.1 ml. of the material and is read in forty eight hours. A positive reaction is similar to a tuberculin reaction. It consists of a papule 0.5 to 1.0 cm. in diameter, surrounded by an erythematous area 3 to 5 cm. in diameter.

Additional laboratory procedures are helpful in establishing a diagnosis of cat scratch disease if antigen for skin testing is not available. Nonspecific lymphadenitis can be excluded by the absence of bacteria in cultures. Cultures of aspirated pus from the lesions of cat scratch disease will not grow tubercle bacilli, and stains for tubercle bacilli are negative. The caseous material present in tuberculous lymph nodes is not seen in the histological examination of lymph nodes of cat scratch disease. If satisfactory cultures of pus from an infected node are obtained, sporotrichosis can be ruled out by its cultural characteristics, and tissue sections stained with periodic acid-Schiff reagent are negative for fungi. Lymphopathia venereum can be excluded by the use of the Frei test. A negative agglutination for Pasteurella tularensis will eliminate the possibility of tularemia.

Every known type of therapy, including numerous antibiotics, has been used in the treatment of cat scratch disease. No form of therapy has been shown to be of curative value, though chloromycetin, aureomycin and terramycin, when given early, may shorten the course of the disease and prevent suppuration.

* * * * *

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REFERENCES

1. Debre, R., Lamy, M., Jammet, M. L., Costil, L., and Mozziconacci, P.: La maladie des griffes de chat, *Bull. et mem. Soc. med. hop.* Paris, **66**: 76, 1950.
2. Daniels, W. B., and MacMurray, F. G.: Cat Scratch Disease; Non-Bacterial Regional Lymphadenitis, *Arch. Int. Med.*, **88**: 736, 1951.
3. Mollaret, P., Reilly, J., Bastin, R., and Tournier, P.: Documentation nouvelle sur l'adenopathie regionale subaigue et spontanement curable, decrite en 1950; La lymphoreticulose benigne d'inoculation, *Presse med.*, **58**: 1353, 1950.
4. Thelin, F., and Martin-du-Pan, R.: New Observations of disease due to cat scratches, *Praxis* (Bern), **40**: 74, 1951.
5. Useri, C., and Hedinger, C.: Ueber die "Maladie des griffes de chat," *Schweiz. med. Wchnschr.*, **81**: 221, 1951.
6. Cassady, J. V., and Culbertson, C. S.: Cat-scratch disease and Parinaud's oculoglandular syndrome. *Arch. Ophth.* **50**: 68, 1953.
7. Stevens, H.: Cat scratch fever encephalitis, *Am. J. Dis. Child.* **84**: 218, 1952.
8. MacMurray, F. G., Sanford, M. C., and Winship, T.: Cat scratch disease simulating sarcoma of the neck, *Am. J. Surg.* **84**: 483, 1952.
9. Wegmann, T., Useri, C., and Hedinger, C.: Die sogennannte Katzenkrankheit, eine benigne Viruslymphadenitis, *Schweiz. med. Wchnschr.* **81**: 853, 1951.
10. Winship, T.: Pathologic changes in so-called Cat-Scratch Fever, *Am. J. Clin. Path.* **23**: 1012–1018, October, 1953.

CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
Assisted by: June Pollack, M.D.
By invitation: Frederic G. Burke, M.D.

This seventeen-month-old white male was admitted with a five-day history of vomiting and dehydration of two days' duration.

One week prior to admission this boy was noted to have a "sweet odor" to his breath and two days later he began to vomit. There was no associated fever or diarrhea and a physician recommended coca cola syrup with sips of tea and gingerale. The following day the physician examined him and found nothing abnormal. On the seventh day of illness flecks of foul-smelling brownish material were noted in the vomitus and he was dehydrated. A tentative diagnosis of intestinal obstruction was made and the patient was hospitalized.

The past history revealed a normal birth and neonatal period. His growth and development were normal. He had been treated with penicillin for occasional upper respiratory infections and on two occasions had diarrhea which responded well to high-protein formulae.

The family history was non-contributary.

Physical examination disclosed a temperature of 101 degrees F., pulse, 150 per minute, and respirations, 45 per minute. The patient was a fairly well-developed, well-nourished male who appeared slightly pale, lethargic and unresponsive. He was lying quietly in bed and had rapid, full respirations. His eyes were turned upward into his head. There was no icterus, the skin turgor was poor and the pharynx was slightly injected. The heart had a normal sinus rhythm without enlargement, murmurs, or thrills. The lungs were clear to auscultation and percussion. The abdomen was soft, non-tender and there was a right upper quadrant, slightly firm mass extending four centimeters below the costal margin from the anterior axillary line to the rectus margin. The spleen was not palpable. Examination of the central nervous system did not reveal any abnormalities.

On admission the urinalysis was acid in reaction and contained acetone. The CO_2 combining power was 16 volumes per cent. A hemogram revealed 9.5 grams of hemoglobin, 3.3 million red blood cells, and 16,000 white blood cells, with 80 per cent polymorphonuclear leukocytes and 20 per cent lymphocytes. A roentgenogram revealed the liver to be enlarged, but there was no evidence of intestinal obstruction. The blood sugar was 235 mgms./100 ml. at 10:30 a.m. on the day of admission to the hospital and at 4:00 p.m. the same day it was 135 mgms.

Seven hundred fifty ml. of M/6 sodium lactate restored the CO_2 to 60 volumes per cent after nine hours. Blood plasma was also given during this period. On the evening of the second hospital day, the temperature suddenly rose to 104 degrees F., the ventricular rate was 250 per minute and a gallop rhythm was present. Diffuse, moist rales were noted in the bases of both lung fields. The extreme lethargy noted on admission had continued and at this time the child became comatose. A consultant in cardiology saw the boy and the tentative impression was myocarditis of undetermined etiology with congestive heart failure. He was digitalized and placed on a maintenance dose of digitalis. He was placed in oxygen, fluids were given intravenously, and penicillin and aureomycin were begun.

He remained comatose and his condition was critical. A systolic murmur developed over the precordium. He had periodic attacks in which he threw his hands

about and had gasping respirations. During these attacks, the heart rate increased to 160/min. but the rhythm was regular. No nuchal rigidity was present. The blood CO_2 combining power on the morning of the third hospital day was 80 volumes per cent, and the non-protein nitrogen was 16 mgms./100 ml. On the evening of the third hospital day, the patient expired during a convulsive episode.

DISCUSSION

Dr. Burke:

On the basis of the information supplied in this brief protocol it would appear that this infant died a chemical death, probably in tetanic convulsion associated with alkalosis. Tetany regularly occurs in hypochloremic states of sufficient duration of any cause. The NPN was reported to be normal the day the baby expired, so in seeking the cause of his acid-base imbalance, occasioned mainly by a great deal of vomiting, we may safely eliminate renal insufficiency.

Vomiting is a symptom that may herald the presence of disease of a heterogenous and polyglot heredity. In this case of dramatic end we can probably say that psychoneurosis played no role and concentrate on organic parentage. It would be of interest to know the nature of the vomiting, was it projectile, copious or colored? We know that it was brownish, indicating digested stomach mucosa—but this is the end result of prolonged emesis common to any cause. Regardless, it was considerable in amount and marked ketosis was a compensatory physiologic change. Vomiting with loss of gastric juice results in a relative increase of sodium available to combine with bicarbonate in the extracellular compartment due to the loss of chloride anion. This is metabolic alkalosis which after prolonged vomiting results in acidosis due to starvation and its accompanying ketosis. Alkalosis of vomiting thus results from chloride deficit with consequent increase in sodium available for combination with bicarbonate.

Potassium moves out of the cell into the blood and since this baby retained no food by mouth for at least seven days, a negative potassium balance developed. While a chloride deficit was similarly present, the potassium loss was more important, because there is two times as much chloride ion in the gastric juice.

Potassium moves out of the cell and is lost through the kidneys and is partially replaced in the cell by sodium. This deficit must be corrected and will persist unless specifically treated: thus the administration of saline solution to these patients can augment the further excretion of potassium by renal activity exaggerating an already potassium-depleted state. The use of any non-potassium containing solution has the same effect, since diuresis augments the electrolyte deficit.

The diuretic effect of M/6 lactate in this baby probably helped to further

deplete the potassium level of the extracellular compartment although correcting the compensatory acidosis. It is noted that plasma and "fluids" were given intravenously the day after his admission, presumably non-potassium containing fluids, thus exaggerating the depletion. By this time the baby was extremely lethargic, weak, and lapsed into coma. The heart dilated and rales were observed in the lung fields. This is the picture of hypopotassemia. Classically in this situation there is progressive weakness and hypotonia of the skeletal musculature progressing to frank paralysis; then dyspnea with gasping respiration in which the accessory muscles of respiration are involved, resulting in cyanosis which is chiefly respiratory in origin but may in part be cardiac; abdominal distention due to atonia, nausea and vomiting and cardiac enlargement with the development of a systolic murmur; increased pulse pressure with corrigan pulse and elevated venous pressure and signs of heart failure. The paralysis of the diaphragm and abdominal muscles and the functional disturbances of the myocardium account for the major clinical signs and symptoms. The electrocardiograph findings are very suggestive and are: (1) slight prolonging of the Q-T interval, (2) decreased height and inversion of T waves, (3) rounded and prolonged T waves, (4) depression of the S-T segment and (5) possible inversion of the P waves, extrasystoles and A-V block.

The terminal phase of illness showed a failing heart, with marked metabolic alkalosis or calcium lack with tetanic convulsion probably represented the final insult. Digitalis will not correct heart failure of this type.

I have approached the solution of this problem from behind and have represented what I believe was the mechanism of the death. I must now try to develop from the available information an adequate reason for the onset of this vicious cycle. Classically this end result can be seen in neglected pyloric stenosis. Of course, this baby was beyond the age group in which this entity is observed and furthermore other causes of high intestinal obstruction are ruled out by the observation of a normal abdomen (except for the palpable mass) and a normal roentgenogram of the belly. On roentgen study the air pattern is observed and the intra-abdominal mass is demonstrated to be a very large liver. Thus volvulus, bands, intussusception, foreign body and other causes of intestinal obstruction are eliminated from consideration. The moderate excess of gas in the intestine is swallowed air and may indicate an early ileus. Further, as we look at the roentgenogram, a normal-size heart and clear lung fields are observed. In view of the cardiac death which ensued two days later this is significant.

It would be attractive to consider for a moment the carbohydrate metabolic defects as a background for this case.

Diabetes is definitely suggested by acidosis and the findings of a blood sugar of 235 mgm. would ordinarily be diagnostic of diabetes, but there is

no glycosuria. Children in diabetic acidosis may present a picture of abdominal pain with vomiting simulating an intestinal obstruction. The liver may enlarge and coma develops rapidly and this sometimes is the initial manifestation of this disease. However, no sugar is reported in the urine, no insulin was given, and five hours after admission a recheck showed a marked reduction to 135 mgm. per cent.

Von Gierke's disease (glycogen storage disease) of the hepatic form might be mentioned although the combined form of liver and heart is not known to exist. Acetonuria is very marked in this condition which represents a carbohydrate deficiency in which glycogen is deposited in various tissues, frequently the liver. Because of some defect in the enzyme system mobilization of this glycogen is resisted. The liver may get very large as the glycogen loads increase but the peripheral glucose blood levels are low. This eliminates glycogen storage diseases and also galactosemia from further consideration.

In any child dying of undiagnosed heart failure, endocardial fibroelastosis must be mentioned, but the roentgenogram of the child two days before death shows a normal-sized heart.

Salicylate intoxication is eliminated only on the basis of the lack of history and indeed would be a leading suspect if this baby had been given aspirin. The lipoid metabolic disorders are eliminated by the absence of splenomegaly.

In order to explain the terminal picture, metabolic imbalance, hepatomegaly, hyperglycemia (in the absence of diabetes) etc., we are forced to examine more closely the central nervous system.

The neurologic examination was said to be normal, but this child was in marked acid-base imbalance. I would like to know whether a spinal fluid examination was made? Hypothalamic stimulation due to lead intoxication, encephalitis, toxoplasmosis, brain tumor and tuberculous meningitis are possible explanations for trigger mechanism which cannot be ruled out entirely on the basis of the information supplied. This cycle could very well have been initiated by such a reflex arc and lacking any other truly adequate information, I would lean to this mechanism as the explanation for this baby's chemical imbalance and death.

PATHOLOGIC DISCUSSION

Dr. Pollack: The students' diagnoses were as follows:

1. Poisoning, specifically lead or salicylate
2. Neoplasm with liver metastases
3. Rheumatic myocarditis
4. Reticulo-endothelial diseases.

Dr. Nestor: Was an electrocardiogram taken?

Dr. Pollack: An electrocardiogram was done on the third hospital day. No report is given on the chart. The only data was the cardiologist's interpretation of myocarditis. The patient was given 0.5 cc. of digitalis nativelli on January 5 and 0.5 cc. on January 6. The electrocardiogram taken on January 7 showed nodal escape with lowering of the ST segments in leads I and II, V_5, V_6. All these changes were believed to be due to digitalis.

Dr. Lopresti: I believe that Dr. Nestor is trying to point out that these electrocardiographic changes as well as the clinical symptoms are seen in cases of hypokalemia. It is rare that these changes represent a digitalis effect unless one is given an overwhelming dose of digitalis. This is not the case in this child. It would seem then, that a disease process is the cause of such a picture.

Dr. Pollack: Very little was known or understood about hypokalemia at the time this child was seen.

Dr. Burke: In 1950–51, not much was written or said about hypokalemia. At a recent potassium conference at the University of Minnesota, Howard Birchell of the Mayo Clinic pointed out that many instances of excessive potassium depletion did not have correlated electrocardiogram abnormalities, and only with very low or very high potassium levels were changes noted in the electrocardiogram.

Dr. Nestor: The serum level of potassium does not represent the extracellular level of the particular electrolyte ion. An individual ion is not the only thing that changes the electrocardiogram. All ions, particularly sodium, have a marked effect.

Dr. Lopresti: I think this case also points out one real lesson. Any youngster who is vomiting, has fever and is lethargic should have a lumbar puncture.

Dr. Pollack: Those are all very good points. I felt a lot could be learned from this case, both from the point of view of what was lacking, as well as from the bizarre clinical picture.

AUTOPSY FINDINGS

Dr. Pollack:

At autopsy, the child was well-developed and well-nourished. The skin and mucous membranes were slightly pale. The heart was moderately enlarged, and the liver extended eight cm. below the right costal margin. The heart weighed one and one-half times normal. The right auricle and right ventricle were markedly dilated, and the left ventricle was slightly hypertrophied. The lungs revealed no abnormality. The liver weighed two and a half times normal. It was yellowish-tan and it cut with increased resistance. The gastrointestinal tract was thoroughly explored and there were no abnormalities seen. Unfortunately, no examination of the cranial cavity was allowed.

Microscopically, the main findings were limited to the liver and the lungs. The liver revealed complete destruction of the normal hepatic architecture, and the lobular pattern was indistinct. The hepatic cells were distended and swollen to the extent that the sinusoids were completely obliterated. The hepatic cells contained many vacuoles, large and small, and the nuclei were compressed against the cell wall. The fatty infiltration was more extensive in the periphery of the lobules. The portal triads were moderately compressed by the dilated hepatic cells, but showed no other abnormalities. The few central veins seen were markedly dilated. The lungs showed some pulmonary edema. The heart, except for the dilation on the right side and the hypertrophy of the left ventricle, revealed no other abnormality.

When the tissues were put into formalin, it was noted that the solution turned a cloudy white. Some liver tissue was put into absolute alcohol, and when these solutions were examined, both the liver tissue and the formalin were found to contain an abnormally high content of glycogen. Special stains of the liver tissue revealed the presence of large quantities of both fat and glycogen.

The final diagnoses in this case were congestive heart failure, both right and left sided; and possible Von Gierke's disease of the liver.

Dr. Burke: I would like you to defend the diagnosis of Von Gierke's disease in this child. The hepatic form of Von Gierke's disease certainly suggests itself on the basis of this very large liver, and particularly where there is some manifestation of a carbohydrate metabolic defect, as evidenced by the unusually high blood sugar level and the acetonuria. However, it is a very predominant and common finding in Von Gierke's disease to have a low peripheral blood sugar level because of an inability to convert glycogen to glucose. Levels of 25, 35, and never more than 45 mgm. per cent are reported in the hepatic form of Von Gierke's disease. Even in the fasting state when large amounts of glucose are given to the child, nothing approximating 235 mgm. per cent blood sugar level reported in this case have been obtained. I can find no good reason to entergain that diagnosis in life on the basis of this protocol.

Dr. Pollack:

On careful scrutiny of the chart, I note that the private physician ordered 350 ml. of 5 per cent glucose in M/6 sodium lactate on admission and that the resident ordered merely M/6 sodium lactate. The nurse's note listed only M/6 lactate given but it is possible that glucose was added. One half an hour after admission, the first blood sugar was done and was 235 mgm. per cent.

Dr. Burke:

Even nine hours later, the blood sugar was 175 mgm. per cent. If this occurs in the hepatic form of glycogen disease, we will have to revise our

ideas on this disease. The major diagnostic point is the characteristically normal or low, and usually very low, blood sugar. The glucose tolerance test usually shows a low blood sugar level initially and the subsequent curve hardly rises at all. I would like to ask Dr. Rice a few questions about the presence of glycogen in liver failure. Does the mere presence of large amounts of glycogen in an obviously knocked-out liver support a diagnosis of Von Gierke's disease? In children dying of hypokalemia the liver shows extensive fatty infiltration and disturbance in glycogenolysis. Potassium is necessary for the metabolism of glycogen and when potassium is not available, glycogen will pile up in the liver, which will cause glycogen storage effects.

Dr. Rice:

I think that Dr. Burke is perfectly justified in doubting the diagnosis in this case. The elevated blood sugars are not expected. However, I cannot recall any liver that caused the formalin solution to become very turbid. Dr. Bessman ran the chemical determination of glycogen and it was unusually high. I remember one other similar case of a child with a large liver and in this case also, the diagnosis of glycogen disease was not thought of either. It is obvious that something else was going on here. If it is glycogen storage disease, it is indeed unusual to get such a high blood sugar level. Neither have I seen any liver such as this one. It is interesting that the chemical composition of various organs in children when one is estimating glycogen, varies considerably. There was an article a year ago about the glycogen content of heart in young children. It shows that in children who have had no cardiac disabilities, the glycogen content of the heart varies remarkably. It is interesting that under conditions in which glycogen piles up in the liver, glycogen leaves the heart. The reverse is also true, namely, that when glycogen is led to the heart, it leaves the liver. In this case, we have the findings visibly, and also the chemical composition of the liver which shows that we are dealing here with a condition which gave an unusually high glycogen content. It is the nearest thing to Von Gierke's disease pathologically and chemically that we have ever had. It is quite proper to question the diagnosis, and as we come up with better understanding of these things, perhaps then we may have a different diagnosis.